Short Report

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Skin Cancer in the Crosshairs

Highlights from the Biennial Scientific Retreat of International Transplant Skin Cancer Collaborative and Skin Care in Organ Transplant Recipients Europe

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Abstract: The International Transplant Skin Cancer Collaborative (ITSCC) is an organization comprising of physicians; transplant surgeons and basic science research scientists dedicated in providing optimal care and ongoing research advancements in solid organ transplant recipients to improve patient outcome and quality of life. As medical advances occur, it is anticipated that the sheer number of solid organ transplantations occurring worldwide will continue to increase. The long-term medication associated immunosuppression improves graft survival, but as a consequence, these individuals become increasingly susceptible to various cutaneous malignancies, lymphoproliferative disorders and infections. Squamous cell carcinoma is the most frequently encountered skin cancer and increases 65- to 250-fold [Jensen et al., Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. *J Am Acad Dermatol*. 1999;40:177-186; Lindelöf et al., Incidence of skin cancer in 5356 patients following organ transplantation. *Br J Dermatol*. 2000; 143:513-519]. However, the rates of basal cell carcinoma, Merkel cell carcinoma and melanoma also increase in organ transplant recipients leading to significant morbidity as well as mortality [Berg and Otley. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. *J Am Acad Dermatol*. 2002; 47:1-20]. In October 2014, the International Transplant Skin Cancer Collaborative and its equivalent European counterpart, Skin Care in Organ Transplant Recipients Europe held its 10th biennial meeting in Essex, MA to discuss the clinical conundrums and the evolving research pertinent to the field. This meeting report provides a synthesis of all the clinical and research data presented at the 4-day meeting.

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President's Overview on International Transplant Skin Cancer Collaborative as an Organization

International Transplant Skin Cancer Collaborative (ITSCC) is an organization comprising of over 600 members worldwide, who are dedicated to the medical and surgical dermatologic care of the organ transplant recipient (OTR).

The meeting held at Essex, Massachusetts in October 2014 was the 10th Biennial meeting of ITSCC and Skin Care in Organ Transplant Recipients Europe (Table 1). It was by open invitation and included clinicians as well as scientists from all around the world including USA, Europe, Australia, and South America, with an interest in transplant dermatology and translational research pertinent to this field. It was sponsored by ITSCC, with Dusa as an industry sponsor. The attendee number was capped at maximum capacity, with preference given to those presenting at the meeting. Two monetary awards were given to fellows in training funded by ITSCC.

One of the main missions of ITSCC is educational outreach. The ITSCC listserv, which allows exchange of information via an email format, is a valuable resource, with regular contribution from 90% of the members on various treatment and management options for OTRs Attendance at the ITSCC retreat, which is held biannually, is felt to be an important avenue to attract members as well as for development and ongoing maintenance of the organization. Future goals for ITSCC include continued educational outreach, collaboration with other specialities including European Skin Care in Organ Transplant Recipients Europe colleagues and more emphasis on mentoring and research initiatives for junior members.

MEETING HIGHLIGHTS

Epidemiology

Prevalence and Risk Factors of Keratinocyte Skin Cancers and Actinic Keratoses

Keratinocyte cancers (KCs), such as squamous cell carcinoma (SCC) and basal cell carcinoma, are the most common

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TABLE 1.

Summary of scientific presentations from the 2014 biennial ITSCC-SCOPE meeting

Epidemiology related to skin cancers	
Study	Findings
Prevalence and risk factors for keratinocyte cancers and AKs in liver transplant recipients	The prevalence of keratinocyte cancers and AKs was noted to be 27% and 89% respectively. History of previous skin cancer was noted to have the most significant association for prevalent KCs and AKs.
Perception of skin cancer risk and behaviors in renal transplant recipients	Education about skin cancer and photo-protection behaviors was provided amongst renal transplant recipients. Increased perceived risk of skin cancer was noted in 78% and improved sun protection behaviors in 38% of participants.
Sun protection behaviors in pediatric population	A multimodal educational intervention regarding skin cancer risk factors and sun protection measures when provided to patients and their guardians showed substantial improvement of these behaviors.
Pathogenesis and future therapies for cutaneous malignancies	
Molecular determinant	Findings
miR-135b mRNA	These are microRNAs that are upregulated in cutaneous SCC. LZTS1 (a tumor suppressor gene) was found to be the potential target gene for miR-135b mRNA. Inhibiting miR-135b resulted in upregulation of LZTS1 mRNA and protein levels and lead to decreased cell motility and invasion of both primary and metastatic cSCC cell lines.
MIT	These are pro-inflammatory cytokine and chemokine that is overexpressed in numerous cancers including human cSCC. Topical application of MIT inhibitor therapy may have a role in therapeutics.
IL-22	IL-22 is a cytokine that induces keratinocyte proliferation which are over expressed in transplant associated SCCs. IL-22 also induces SCC proliferation in vitro.
miR-21, miR-205, let-7b and miR-498	Target messenger RNAs (mRNAs) that appear to be important in the progression from chronically irradiated skin to AK to cSCC.
Melanoma	
Pretransplant melanoma	Noted to have increased risk for overall and melanoma-specific mortality after transplantation.
Merkel cell carcinoma	
MHC Class I	Downregulation of MHC Class I lead to poorer prognosis in patients with Merkel cell carcinoma. Treatment with interferon *in vitro* and *in vivo* rescues MHC expression.
Squamous cell carcinoma	
ITSCC-SCOPE PAIN Study	Pain has been recognized as the most consistent sign of invasiveness in a collaborative multi-center study involving 10 countries.
Non-neoplastic complications	
GVHD	Patients who have had liver or bowel transplants are at greatest risk of developing GVHD. The cutaneous inflammation induced by chronic GVHD may further contribute to the formation and evolution of cutaneous malignancy in OTRs.

SCOPE indicates Skin Care in Organ Transplant Recipients Europe

malignancies in fair-skinned OTRs.[1,2] Actinic keratoses (AKs) are acquired lesions that are characterized by a proliferation of atypical keratinocytes beginning in the basal layer[3] and confined to the epidermis.[4] They are commonly encountered in fair skinned OTRs and are known surrogate markers for skin cancer risk.[5] Collectively, these actinic lesions cause significant morbidity-, mortality-, and health-related costs.[6,7] Dr Sinnya presented preliminary data from a cross-sectional study of 183 liver transplant patients from the Princess Alexandra Hospital in Queensland, Australia (Table 2). This study reviewed the baseline prevalence of both KCs (SCC, basal cell carcinoma and Bowen disease) and AKs to gain an insight into the current disease burden. The study demonstrated that the baseline prevalence of KCs was 27%; quite high in comparison to the reported cumulative incidence in the literature ranging from 7% to 16% at 5 and 10 years after liver transplantation.[8] Eighty-nine percent also had 1 or more AKs demonstrating a sizeable disease burden in this population. When dissecting the risk factors, history of previous skin cancer appeared to be the most significant for future skin cancers. As per the previous transplant literature, fair skin type, history of increased sun exposure, history of AKs, and older age were also some of the comparable risk factors identified for KCs and AKs, highlighting the need to target some modifiable risk factors to minimize the aftermath associated with these conditions.

Primary Prevention Measures in OTRs

Given the increased burden of skin cancers in OTRs worldwide, ongoing education regarding adoption of collective behaviors that reduce this burden is warranted.[9] Dr Timothy Chang presented his study, which looked at questionnaire data on 666 renal transplant patients from Froedert Memorial Lutheran Hospital in Wisconsin. Seventy-eight percent of the patients from this study reported increased perceived risk of skin cancer after transplantation, and 38% had improved sun protection behaviors (use of long sleeves, hats, and sunscreen) after transplantation. However, 59% had no improvement in sun protection behaviors. He highlighted that although there was only modest improvement in sun protection behavior before to after transplant, a significant improvement in perceived risk for skin cancer was seen compared to previous studies. Methods to increase ongoing education about sun protection behaviors and skin cancer risk perception is therefore paramount in these patients and should be encouraged.

In the pediatric solid OTRs, skin cancers, and lymphoproliferative disorders, like the adults, also remain the most common malignancies.[10] Dr Carrie Coughlin presented data on sun protection practices in the pediatric population. In this study, patients and their guardians were surveyed about their knowledge regarding skin cancer risk factors and sun protection measures, then provided with a multimodal educational

TABLE 2.

Details of the presenters and presentations from the 10th biennial meeting at Essex

Sarah Arron, MD, PHD
UCSF Dermatologic Surgery and Laser Center, California, USA
"Increased mortality in transplant recipients with a history of pretransplant melanoma"
Jan Nico Bouwes-Bavink, MD, PHD
Leiden University Medical Centre, Leiden, Netherlands
"Pain Study update"
John Carucci, MD, PHD
NYU Lagone Medical Centre, New York, USA
"Cyclosporine A polarizes T cells toward T22 and induces IL-22 receptor in human SCC cells in vitro: a mechanism driving IL-22 induced SCC proliferation"
Timothy Chang, MD
Mayo Clinic, Rochester, USA
"Perception of skin cancer risk and sun protection behavior in renal transplant recipients"
Carrie Coughlin, MD
Children's Hospital of Philadelphia, Philadelphia, USA
"Skin cancer awareness and sun protection in pediatric solid organ transplant recipients"
Victor Huang, MD
Brigham and Women's Hospital, Boston, USA
"Downregulation of surface class I major histocompatibility complex is associated with poor prognosis in Merkel cell carcinoma patients and is reversible with interferon treatment"
Anoki Jambusaria, MD
Mayo Clinic, Rochester, USA
"Databasing"
Zelmira Lazarova, MD
Edit Olasz, MD, PHD
Medical College of Wisconsin, Milwaukee, USA
"MicroRNA-135b regulates expression of leucine zipper tumor suppressor 1 in cutaneous squamous cell carcinoma"
Tania Oberyszyn, MD, PHD
Ohio State University, Columbus, USA
"A preclinical model of immunosuppressive drug driven NMSC"
Walmar Oliveira, MD, PHD
Department of Dermatology, University of Sao Paulo, Sao Paulo, Brazil
"Two cases of phaeohyphomycosis in renal transplant patients"
Manisha Patel, MD
Johns Hopkins Hospital, Baltimore, USA
"Molecularly targeted therapies for cancers in SOTRs"
Charlotte Proby
Jaqui Wood Cancer Centre
"Actinic keratoses and field change and their associations with squamous cell carcinoma in renal transplant recipients in Manchester
Arturo Saavedra, MD, PHD
Massachusetts General Hospital, Boston, USA
"GVHD after solid organ transplantation"
Chrysalyne Schmults, MD
Dana Farber/Brigham and Women's Cancer Center, Boston, USA
"Databasing"
Sudipta Sinnya
University of Queensland
"Keratinocyte cancers and actinic keratosis in liver transplant recipients in Queensland
Myrto-Georgia Trakatelli, MD, PHD
Aristotle University of Thessaloniki, Thessaloniki, Greece
"Using the Fitzpatrick classification for sun-reactive skin types in studies: possible pitfalls"
Kenneth Tsai, MD, PHD
Texas MD Anderson Center, Houston, USA
"Genomic drivers of cutaneous squamous cell carcinoma development"

intervention. Follow-up surveys showed that patients and their guardians benefited from the education, with substantial improvement of some of these behaviors. Her future work will be geared toward both creation and promotion of pediatric-specific educational materials as well as development of more targeted tools to assess the outcome of future educational interventions

Secondary Prevention Measures

Coupled with primary prevention, secondary prevention measures are of utmost importance in both pediatric and adult OTRs. Adherence to the ITSCC skin surveillance guidelines will allow early recognition and management of suspicious lesions with worrying clinical symptoms and signs, such as pain, rapid enlargement, and bleeding.[11-13] Pain has also been recently confirmed as the most powerful warning sign for invasive SCC. Dr Bouwes Bavinck discussed the findings of a collaborative study between 10 countries, which looked at clinical symptoms of SCC in OTRs. They found pain to be the most consistent clinical symptom associated with invasiveness.[14]

Graft-Versus-Host Disease

Dr Arturo Saavedra discussed the complications associated with graft-versus-host disease (GVHD) in OTRs. Compared to hematologic transplantation, solid organ transplant-associated GVHD can carry a worse prognosis. Patients who have had liver or bowel transplants are at greatest risk of developing GVHD and the mortality has been reported to exceed over 80% in some cases.[15,16] Dr Saavedra emphasized that the dermatologist is central to making the diagnosis of GVHD, which often can be elusive as histopathology may be non-specific and serologic markers are not available. In addition to suffering from potential increased phototoxicity and increased immunosuppression after transplantation, the level of cutaneous inflammation induced by chronic GVHD may be an independent, added etiologic factor contributing to the formation and evolution of cutaneous malignancy.

Melanoma

Melanoma remains the most life-threatening cutaneous malignancy in the OTRs.[17] The survival rates in the immunocompetent patients have been well documented and vary depending on the disease stage as per American Joint Committee on Cancer staging classification. Breslow's microscopic tumor thickness is the most important prognostic factor, but presence of other microscopic features also indicates poor survival such as ulceration, mitoses, regression and tumor infiltrating lymphocytes.[18] It has been noted in the transplant literature that the 5-year survival of post transplant melanoma is similar to that of the American Joint Committee on Cancer population for T1 and T2 (≤2 mm) but significantly worse for higher tumor stages.[19] To date, there have been a paucity of studies that have reviewed the survival data on OTRs with pretransplant melanoma. Dr Sarah Arron from University of California in San Francisco presented data from the National Cancer Institute Transplant Cancer Match Study demonstrating that transplant recipients with pretransplant melanoma have increased risk for overall and melanoma-specific mortality after transplantation.

Surgical excision remains the mainstay of melanoma management also in OTRs Typically, a 1 cm margin is recommended for "thin" melanomas (<1 mm) and 1 to 2 cm for thicker tumors. Sentinel lymph node biopsy is also recommended for tumors greater than 1 mm thick or thinner melanomas with poor prognostic indicators.[20] Advancements in the treatment of metastatic melanoma also remain promising with the development of signaling pathway inhibitors (B-Raf proto-oncogene, mitogen activated protein inhibitors) and immunotherapies such as anti-CTLA4 and anti-PD1 antibodies.[20]

Genetics of Skin Cancers

The advancement in genomic medicine is a stepping stone to better understanding the genetics of skin cancers. Dr Ken Tsai gave an insightful talk on genetics of cutaneous SCC (cSCC) highlighting that alterations in microRNA (miRNA) expression drive key aspects of cSCC development. Applying miRNA-sequence, RNA sequence, and exome sequence to matched human and mouse samples of skin, AKs, and cSCC, his team have identified a core set of miRNAs and their target messenger RNAs (mRNAs) that appear to be important in the progression from chronically irradiated skin to AK to cSCC. These include miR-21, miR-205, let-7b, and miR-498 and their associated targets, which regulate cell cycle progression, apoptosis, cellular motility, and tumor cell metabolism. His laboratory is in the process of validating these findings in cSCC cell lines and testing to see whether in vivo manipulation of their expression can be used as an avenue to prevent cSCC development.

Future of Therapeutics

Squamous Cell Carcinoma

Squamous cell carcinoma is the most common KC found in OTRs.[21] They usually present as keratotic plaques, papules, or nodules but can also rarely present as ulcerative and exophytic lesions which can often be unsightly as well as painful.[22] Currently, destruction versus surgical removal of SCC remains the mainstay of treatment. However, with emerging molecular mechanisms being defined, molecularly targeted, and immune system-based therapies may in the near future complement current treatment options.

Dr Edit Olasz and Dr Zelmira Larazova discussed the potential role of miRNAs as targeted drug treatment option for cutaneous SCC. The miRNAs are epigenetic regulators of gene expression and play an important role in tumor growth and metastasis. Recently, miRNAs have emerged as new therapeutic targets for cancer treatment, but their utility in cSCC treatment remains to be elucidated. Olasz and Zelmira analyzed the differential expression of 88 cancer-related miRNAs in 43 study participants with cSCC and 15 nonlesional skins by microarray analysis and quantitative real-time polymerase chain reaction. miR-135b was the most upregulated miRNA and in silico screening identified leucine zipper putative tumor suppressor 1 (LZTS1) as potential target gene of miR-135b. Immunohistochemical evaluation of cSCC tumor tissues (n = 50) demonstrated that miR-135b mRNA expression inversely correlated with staining intensity of LZTS1 in the tumor cells. Functional studies inhibiting miR-135b in three cSCC cell lines resulted in upregulation of LZTS1 mRNA and protein levels and lead to decreased cell motility and invasion of both primary and metastatic cSCC cell lines. In contrast, miR-135b overexpression induced further down-regulation of LZTS1 mRNA in vitro. Their research findings provide exciting insight into the molecular mechanism by which the oncogenic miR-135b regulates LZTS1 in cSCC and suggest that miR-135b may be used as a molecular target for the development of new treatment strategies for cSCC.

Dr Tatiana Oberyszyn discussed the possible role of macrophage migration inhibitory factor (MIF) for treatment of cSCC. Macrophage migration inhibitory factor is a proinflammatory cytokine and chemokine that is overexpressed in numerous cancers, including human cSCC.[23] Dr Oberyszyn further plans to determine the efficacy of a topical application of MIF inhibitor before initiation of an immunosuppressive (tacrolimus + mycophenolate mofetil) regimen on ultraviolet B–induced cutaneous tumors and also review its possible role of MIF in established cutaneous tumors under the immunosuppressed environment.

Dr John Carucci from NYU-Langone Medical Centre discussed the role of interleukin-22 (IL-22) in the pathogenesis of aggressive SCC in OTRs. Given that IL-22 is a cytokine that induces keratinocyte proliferation, his team explored whether SCC microenvironment showed increased IL-22 and how this correlated with SCC proliferation. Immunohistochemistry revealed that IL-22 mRNA expression was increased for SCC along with IL-22 and IL-22 receptor (IL-22R) positivity. Moreover, T-cell profiles of tumor cultured from aggressive transplant-associated SCC (TSCC) differed from those of immunocompetent patients with SCC. The TSCC showed an increase in IL-22 producing Tc22 cells and decrease in IFN-γ–producing CD8+ cells and further demonstrated that IL-22 also induced SCC proliferation in vitro. Hence, IL-22 may have a role in management of aggressive TSCC in the near future by serving as an exciting new therapeutic target.

Merkel Cell Carcinoma

Merkel cell carcinoma (MCC) is a neuroendocrine tumor that predominantly occurs in elderly patients in sun-exposed sites, occurring as firm, violaceous nontender papules or nodules.[24] The MCC is more common in OTRs with a 10-fold increase in incidence compared to the general population.[25] Prognosis is dependent on disease extent but generally poor with 68% of head and neck cases metastasizing to lymph nodes and causing death in 56%.[26] Treatment for MCC currently comprises of wide local excision for local disease. Sentinel node biopsy (with/without a neck dissection) and adjuvant radiation to the primary site and affected lymph node is recommended.[26]

Dr Victor Huang discussed the role of surface class I major histocompatibility complex (MHC) in MCC and that its downregulation may lead to poor prognosis. Immunohistochemistry evaluation of tumors from 73 patients performed by this group revealed 62% had a deficiency of MHC I expression associated with a 3.25-fold greater risk of death. Real-time polymerase chain reaction and flow cytometry confirmed these results in validated Merkel polyomavirus as well as cell lines, both in vitro and in vivo. Treatment with interferon in vitro and in vivo rescued MHC expression. Dose-response experiments indicated that IFN-γ or -β are much more potent inducers of MHC than IFN-α used in previous cases of MCC therapy. Dr Huang foresees that as immunomodulatory therapies, such as checkpoint blockade and adoptive cell transfer,

become available, these modalities may have synergistic effects with modalities that rescue MHC I expression on MCC.

FUTURE PERSPECTIVES

Given the plethora of cutaneous complications in OTRs, ongoing research and collaboration between clinicians and researchers is essential to better understand the underpinning disease pathogenesis. In the recent years, major efforts have been made to gain better insight into the molecular mechanisms and genetics of cutaneous malignancies in OTRs. This in turn has shed light on some exciting new possibilities for therapeutic developments that was shared in this Meeting. Molecular targets such as miR-135b may serve a role in cSCC treatment, as may topical MIF inhibitor prior initiation of immunosuppressive therapies. Cytokines, such as IL-22, that appear to be expressed in aggressive SCCs may also serve as exciting novel therapeutic targets. Ongoing research in this field will hopefully allow these ideas to be trialed and their applicability tested in a clinical setting.

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